

REMARKS

Claims 1-25 and 58-60 are pending with entry of this amendment. Claims 26-57 are cancelled without prejudice to subsequent renewal, pursuant to the restriction requirement portion of the Action. Claims 58-60 are added herein. Claims 1, 3-5, 9, 11 and 22-23 are amended herein. The amendments and new claims introduce no new matter and support for the amendments is replete throughout the specification and claims as filed. These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record. Applicants submit that no new matter has been added to the application by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

The Action included a restriction requirement, Objections to the Specification, a double patenting rejection over copending application USSN 10/126,927, rejection of the claims for alleged indefiniteness, anticipation and obviousness. To the extent that any of these rejections or objections are applied to the amended claims and specification, Applicants traverse for the reasons noted herein.

For convenience, the following remarks address the Action Items in the order presented in the Action.

RESPONSE TO RESTRICTION (ACTION ITEMS 1-9)

Applicants confirm their election of group I, claims 1-25. Applicants note that this election is with traverse. The basis for Applicants' traversal is with respect to unelected groups 7 and 9. The restriction of separate sequences falling within the scope of claims 55 and 57 in these groups into further restriction groups does not meet with the requirements for restriction set forth by MPEP § § 803.02 and 803.04. Further, the Courts have forbidden all forms of misjoinder rejection under 35 USC § 121. See, e.g., In re Weber 198 USPQ 328, In re Haas 198 USPQ 334 and In Re Harnish 206 USPQ 300. Accordingly, while this issue is moot in the subject case in light of the group that Applicants have elected, Applicants reserve the right to traverse the restriction in any unelected group in one or more divisional, continuation or other continuing application(s).

PRIORITY (ACTION ITEM 10)

Applicants note with appreciation the Examiner's acknowledgement of the priority claim.

INFORMATION DISCLOSURE STATEMENT (ACTION ITEM 11)

Applicants note with appreciation the Examiner's indication that the IDS of April 2, 2004 is being considered. Applicants request that the Examiner provide signed and initialed 1449 forms indicating consideration of the references.

SPECIFICATION (ACTION ITEM 12-13)

The specification was objected to for containing browser executable links. The above amendments to the specification render the links unexecutable. Accordingly, the objection should be withdrawn.

DOUBLE PATENTING (ACTION ITEMS 14-16)

Claims 1 and 23-25 were rejected for alleged obviousness-type double patenting over claims 48 and 84 of copending application USSN 10/126,927. Applicants note that this rejection is moot in light of amendments to USSN 10/126,927 which have deleted claims 48 and 84 in that case. However, Applicants also respectfully note that the rejection does not set forth how the specific limitations of the claims in each case are obvious in light of one another. That is, to set forth a *prima facie* case for obviousness in a double patenting context, it must be shown how the claims can be considered obvious in light of each other (and one-way nonobviousness is all that is required for separate patentability; *see, Winter v. Fujita*, 53 USPQ2d 1234, 1243 (Bd. Pat. Interferences 1999), *reh'g denied*, 53 USPQ2d 1478 (Bd. Pat. Interferences 2000)). The limitations of the claims at issue must be addressed in such a rejection. The rejection does not do this, arguing that "they are not patentably distinct because Schultz P et al. discloses a method of using a translation system with an orthogonal aminoacyl tRNA synthetase to produce at least one protein comprising at least one unnatural amino acid." This does not set forth how the actual limitations of the claims at issue are related and, accordingly, the rejection does not establish a *prima facie* case of obviousness-type double patenting. Accordingly, in light of the deletion of the relevant

claims from USSN 10/126,927 and the Action's failure to establish a *prima facie* case, the rejection must be withdrawn.

THE CLAIMS, AS AMENDED, ARE DEFINITE (ACTION ITEMS 16-22)

The Action rejected claims 1-25 for alleged indefiniteness. To expedite prosecution, Applicants have amended the claims to overcome certain of the rejections; however, to the extent any of the rejections may be applied to the amended claims, Applicants traverse for the reasons noted below.

Claims 3 and 9 were rejected for use of "keto" rather than "ketone" moiety. Applicants have amended the claims as helpfully suggested.

Claim 11 was rejected for use of the phrase "other reactants." This superfluous language has been deleted.

Claim 23, 24 and 25 were rejected for use of the term "preferentially" and "orthogonal tRNA synthetase" in claim 23. The term "preferentially" is specifically defined in the specification at paragraph 23. However, to expedite prosecution, the term has been deleted from claim 23. The term "orthogonal" is defined at paragraph 22. Moreover, the specification as a whole and the art in general are entirely clear as to what an orthogonal synthetase is, i.e., it is a synthetase that efficiently charges an orthogonal tRNA with an amino acid in a translation system, while at the same time not efficiently functioning with endogenous components of a given translation system (e.g., displaying little or no ability to aminoacylate a cell's natural complement of tRNAs as compared to its ability to aminoacylate a corresponding orthogonal tRNA). Because the term is defined, extensively described in the specification and is in wide use in the relevant literature in the field, there can be no argument that the term is indefinite.

Claim 25 was rejected for alleged indefiniteness in the use of the term $\text{mutRNA}_{\text{CUA}}^{\text{Tyr}}$. Applicants have added SEQ ID NO. 7, as suggested, to further clarify the term.

Claims 1-25 were rejected for allegedly omitting essential steps. The Action argues that one must purify the glycoprotein before it can be known that one is produced. Applicants traverse this rejection. While purification of a glycoprotein produced in the

method is certainly within the scope of the claims (*see, e.g.,* Example 3), and is expressly claimed, *e.g.,* in claim 60, it is not *necessary* in determining whether a glycoprotein is produced. There are a variety of specific detection methods that can be performed on either purified or unpurified glycoproteins, *e.g.,* detection of binding by ligands such as proteins that specifically bind a glycoprotein of interest, detection of labels that are incorporated into the carbohydrate or unnatural amino acid moieties of the glycoproteins, or the like.

For example, antibody-based detection of produced glycoproteins can be performed. In addition to one of skill being aware of this common approach to the specific detection of proteins, which can be performed *in vitro*, *in situ*, or *in vivo*, on purified or unpurified components, the specification also provides considerable guidance in this respect. *See, e.g.,* paragraphs 78-87 and *e.g.,* paragraph 115. Similarly, detection can, of course, be performed by monitoring binding or enzymatic activity of any of a variety of carbohydrate-specific binding proteins or enzymes. This approach is also taught in the specification. *See, e.g.,* paragraph 225. As noted, any sugar moiety can also be labeled and incorporation into a protein can be determined, without purification, using any of a variety of common methods, such as FRET, fluorescence polarization, or the like. *See also*, paragraph 206. Clearly, glycoprotein detection can be performed *in vitro* or *in vivo*, on purified or unpurified components. The specification teaches all of these approaches and one of skill is certainly aware of a variety of such detection methods that do not require purification. Accordingly, the rejection must be withdrawn.

AS AMENDED, THE CLAIMS ARE NOT ANTICIPATED (ACTION ITEMS 23-24)

Claims 1-7, 10-13 and 21 were rejected for alleged anticipation by Rodriguez et al. To the extent this rejection is applied to the amended claims, Applicants traverse.

Claim 1 has been amended to require that the reactive group be incorporated into the protein in a translation system. Rodriguez provides an entirely unrelated approach, in which short synthetic peptides comprising a ketone are chemically synthesized on a solid phase support. Because Rodriguez does not provide the limitations of the claims, as amended, the rejection must be withdrawn.

AS AMENDED, THE CLAIMS ARE NOT OBVIOUS (ACTION ITEMS 25-27)

Claims 1-21 were rejected for alleged obviousness over Rodriguez in combination with Palcic, in view of Kaushal. To the extent that the rejection is applied to the amended claims, Applicants respectfully traverse.

As noted above, claim 1 has been amended to require that the reactive group be incorporated into the protein in a translation system. Nothing in Rodriguez, Palcic or Kaushal provides this limitation. Accordingly, the combination of references does not provide the limitations of the amended claims, and the rejection must be withdrawn.

Because this is alone sufficient to overcome the rejection, issues of motivation and reasonable expectation of success need not be addressed in detail at this time. Applicants also note, however, that the rejection alleges a general, rather than a specific motivation for the proposed combination, which is insufficient to establish a *prima facie* case of obviousness. MPEP 2143.01. Furthermore, the rejection does not address issues of expectation of success, which is also required in establishing a *prima facie* case for obviousness. MPEP 2143.02.

For these reasons as well, the rejection must be withdrawn.

AS AMENDED, THE CLAIMS ARE NOT OBVIOUS (ACTION ITEM 28)

Claims 1-25 were rejected over Rodriguez et al. in view of Palcic and Kaushal, and further in view of Wang. Applicants traverse.

As noted above, claim 1 has been amended to require that the reactive group be incorporated into the protein in a translation system. Wang et al. provide a pioneering system for incorporating unnatural amino acids into proteins using orthogonal components. However, no motivation or expectation of success can be found in the combination of references alleged in the rejection.

The Rejection Does Not Show how One of Skill Would Have had Reasonable Expectation of Success

As set forth in the MPEP at 2143.02, a reasonable expectation of success must exist before references can be combined to establish a case for obviousness. The rejection fails even to allege how a reasonable expectation of success can be found in the proposed combination of references and the rejection is insufficient on this ground alone.

For example, the rejection does not establish how one of skill could have had any expectation that an appropriate orthogonal synthetase could be constructed to insert an unnatural amino acid comprising a reactive group that was appropriate for coupling to a carbohydrate. Without experimental evidence as to whether such a synthetase could be made, there was no way to know whether the relevant unnatural amino acid could be specifically inserted by a translation system comprising the relevant orthogonal elements.

That is, the rejection has not established how one of skill could have known whether, for example, an unnatural amino acid comprising a ketone or other reactive group could be charged onto a tRNA by a synthetase, whether the translational machinery could function to incorporate the group, whether the reactive group would react undesirably with other components of the translational system (e.g., cognate reactive groups naturally present in the cell or other translation system), etc. Without a reasonable expectation that each of these technical issues could be overcome, no expectation of success could have existed prior to the present invention for the proposed combination of references.

No Specific Motivation for the Combination of References Is Provided

There is no *specific* motivation articulated in the rejection for making the proposed combination of references. For example, the Rodriguez system is fundamentally unrelated to incorporation of unnatural amino acids by a translation system, or even to production of proteins by such a system as taught by Wang. Rodriguez relates to a purely chemical synthetic approach to making a simple glycosylated polypeptide via a solid phase synthetic method. With respect to motivation to combine this reference with Wang, the rejection alleges that one of skill would have been motivated to substitute a completely different technology, i.e., in vivo incorporation of unnatural amino acids, to achieve the present invention, because one of skill was aware “that glycoconjugates participate in a wide range of physical processes” (Action item 27). This is a statement as to the general desirability of work in the field of glycoconjugates, but it provides no indication at all as to why one of skill would have combined the *specific* references at issue. This difference between *general* motivation to perform work in an area of research and *specific* motivation to combine particular references, is clearly set forth in the MPEP and the case law relating to obviousness.

As the MPEP sets forth, “Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching suggestion or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art.” MPEP 2143.01. As the Courts have clearly stated, this means that the Patent Office “must explain why one of ordinary skill in the art would have been motivated to select references and to combine them to render a claimed invention obvious.” Moreover, as the Court stated with respect to the type of evidence of motivation that must be presented by the Office, “the need for specificity pervades this authority. ‘Particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.’” In Re Lee 61 USPQ 1430 at 1433, (Fed Cir. 2002), *citations omitted*.

Put another way, the motivation articulated in the rejection for the combination of references is equally applicable to *all* research in the field of glycoconjugates. This sort of general motivation to perform research in a technical field is completely unrelated to the concept of specific motivation to combine *particular* references to provide a particular invention. The reason for this distinction between general motivation and specific motivation is straightforward—if the Office were permitted simply to rely on such general motivation to combine references, then *all* combinations, with the benefit of hindsight, would be motivated. This is clearly not the law.

In summary, no motivation for combining Wang and Rodriguez or the secondary references Palcic and Kaushal is found in the references or the art. The Action has not alleged any specific motivation for the proposed combination of references that can be drawn from the references or the art. Furthermore, no expectation of successfully combining these references can be found in the references or the general state of the art.

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Reply to Office action of August 31, 2004

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the claims are deemed not to be in condition for allowance after consideration of this Response, an interview with the Examiner is hereby requested **prior to preparation of any additional Action by the Office**. Please telephone the undersigned at (510) 337-7871 to schedule an interview.

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Respectfully submitted,



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Attachments:

- 1) A transmittal sheet; and,
- 2) A receipt indication postcard.